

Treatment of Psychotic Symptoms in Parkinson's Disease

Felix-Martin Werner^{1,2,*} and Rafael Coveñas²

¹Higher Vocational School of Elderly Care and Occupational Therapy, Euro Academy, Pößneck, Pößneck, Thuringia, 07381, Germany

²Laboratory of Neuroanatomy of the Peptidergic Systems (Lab. 14), Institute of Neurosciences of Castilla y León (INCYL), University of Salamanca, Salamanca, Castilla-León, 37007, Spain

*Corresponding author: Felix-Martin Werner, University of Salamanca, Instituto de Neurociencias de Castilla y León (INCYL), Laboratorio de Neuroanatomía de los Sistemas Peptidérgicos (Lab. 14), c/ Pintor Fernando Gallego, 1, 37007-Salamanca, Spain, Tel: +34/923/29 44 00, extn. 1856; Fax: +34/923/29 45 49; E-mail: felixm-werner@versanet.de

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Abstract

The treatment of Parkinson's disease with l-dopa and a decarboxylase inhibitor, with dopamine agonists or with NMDA antagonists can cause psychotic symptoms. Neural networks are described in the mesolimbic system in order to explain this adverse effect. The psychotic symptoms are treated with second-generation antipsychotic drugs which do not worsen movement disturbances. Among these drugs, the administration of clozapine and quetiapine is recommended to treat psychotic symptoms in Parkinson's disease.

Keywords: Parkinson's disease; Psychosis; Second-generation antipsychotic drugs; Dopamine; Serotonin; Clozapine; Quetiapine

Introduction

Parkinson's disease is a neurodegenerative disease with a dopamine and GABA deficiency and a glutamate and acetylcholine surplus in the extrapyramidal system [1]. A pharmacological treatment is started, if the symptoms rigidity, akinesia and tremor appear [1]. The disease is treated with l-dopa and a decarboxylase inhibitor which increase dopamine levels in the extrapyramidal system, i.e. substantia nigra and putamen, or with dopamine agonists which activate dopamine receptors, especially the D₂ receptor [1]. If movement disturbances get worse, NMDA antagonists, for example amantadine can be administered as an additional therapy. Glutamatergic neurons inhibit presynaptically D₂ dopaminergic neurons in both the putamen and the substantia nigra and activate M4 cholinergic neurons in the putamen [2]. Therefore, an NMDA antagonism improves dopamine deficiency via D₂ receptors and an acetylcholine surplus via M₄ receptors [2]. As a consequence of the described pharmacological treatment, Parkinsonian patients can show psychotic symptoms during the course of the treatment [3]. Several questions arise, why these pharmacological agents can cause these psychiatric symptoms and how to treat adequately psychosis in Parkinson's disease [3].

Neural Networks in the Mesolimbic System

In order to answer the questions why anti-Parkinsonian drugs can cause psychotic symptoms and how to treat adequately these symptoms, neural networks are described in the mesolimbic system [3]. In this system, GABAergic neurons weakly inhibit dopaminergic neurons via GABA_A receptors and thus allow a high dopamine activity. Dopaminergic neurons are connected via D₂ receptors to glutamatergic neurons, which weakly inhibit serotonergic neurons via NMDA receptors. Serotonergic neurons exert a high activity, via 5-HT_{2A} receptors, and are connected to GABAergic neurons. In the A10 cell group, dopaminergic and serotonergic neurons activate each other via D₂ or 5-HT_{2A} receptors.

L-dopa and a decarboxylase inhibitor or dopamine agonists can lead to psychotic symptoms in Parkinsonian patients during the course of the treatment, because they increase dopamine levels in the mesolimbic system and cause dopamine hyperactivity. NMDA antagonists can cause psychotic symptoms as well, because a reduced glutamatergic inhibition via NMDA receptors of 5-HT_{2A} serotonergic neurons in the mesolimbic system can cause 5-HT_{2A} serotonin hyperactivity [4]. Psychosis occurs in 20 to 40% of Parkinsonian patients. These symptoms worsen patients' quality of life. The most frequent psychotic symptoms are visual hallucinations [4]. Another strategy to improve psychotic symptoms is to reduce the dosage of the anti-Parkinsonian drugs [4].

Results

If Parkinsonian patients develop psychosis, second-generation antipsychotic drugs (SGAs) are administered. The following SGAs are preferred, because they do not worsen movement disturbances [4] (Figure 1):

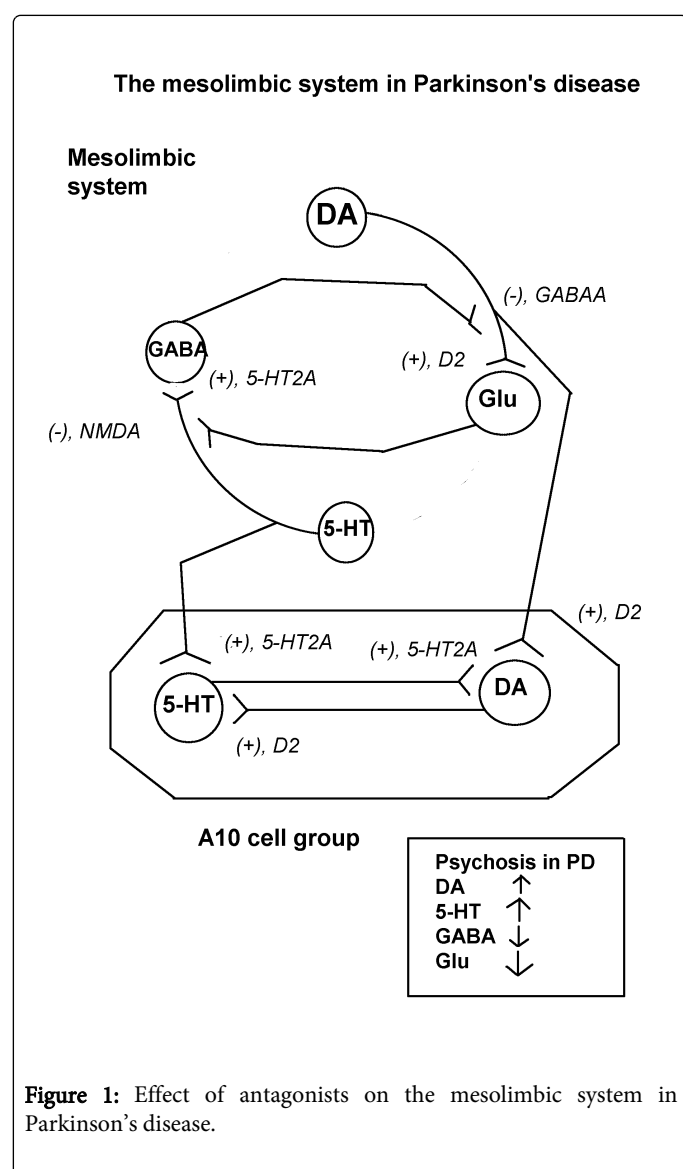
- Clozapine, which blocks D₃, D₄ and 5-HT_{2A} receptors and does not interfere with movement disturbances.
- Quetiapine, which weakly blocks D₂ receptors and exerts the main antipsychotic effect by blocking 5-HT_{2A} receptors.

The adverse effects of clozapine are: the development of type two diabetes mellitus, an increase in blood pressure, weight gain and agranulocytosis (this appears in 3% of patients). The adverse effects of quetiapine are: an increase in the level of blood sugar, an increase in blood pressure and the appearance of a cardiac heart disease [5,6].

Discussion

Psychotic symptoms, above all visual hallucinations occur in 20 to 40% of the Parkinsonian patients treated with dopaminergic or anti-glutamatergic anti-Parkinsonian drugs [2-5]. These psychiatric symptoms are treated with SGAs. Among these SGAs, clozapine and quetiapine are the drugs of choice, because they do not worsen movement disturbances [2,4-6]. The adverse effects, above all

metabolic effects, can again deteriorate patients' quality of life [6]. Novel options in the treatment of Parkinson's disease can be suggested: for example, to combine l-dopa and a decarboxylase inhibitor or dopamine agonists with 5-HT_{2A} receptor antagonists, which improve the motor symptoms and do not cause psychotic symptoms, but exert a slight antipsychotic effect [1]. Because 5-HT_{2A} antagonists improve motor symptoms by increasing dopamine levels in the putamen through a reduced presynaptic glutamergic inhibition via NMDA receptors and because in the mesolimbic system these antagonists exert a slight antipsychotic effect through an 5-HT_{2A} receptor antagonism, they are less likely to produce psychotic side effects in combination with l-dopa or dopamine agonists. In the mesolimbic system, NMDA antagonists are likely to produce psychotic symptoms, because they induce serotonin hyperactivity through a reduced presynaptic inhibition.



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